REMARKS/ARGUMENTS

The applicants submit the following remarks to address the Examiner's rejection which taken in combination with the amendments presented herewith attempt to address each of the Examiner's concerns.

Claims 130, 132, 133, 136, 137 and 140-142 are pending with claim 130 being independent. Claims 131, 134, 135, 138 and 139 have been cancelled. Claims 130, 132, 136 and 141 have been amended. Claim 130 has been amended to more particularly and distinctly define the invention so as to overcome the technical rejection and to define the invention patentably over the prior art. Support for the amendment to claims 130 is found in previous claims 130, 131 and 135; in the published application at page 2, paragraph [0014], [0015]; page 3 para [0032]; Page 5 [0044] and examples 1-6, and 8-13. Claims 132 and 136 are amended to correct the dependencies. Support for the amendment to claim 141 is found in the published application at page 3, paragraph [0027].

Election/Restriction

Examiner maintained the election/ restriction rejection stating that there is no evidence on record that the water miscible organic solvents enlisted are obvious variants of each other.

Applicants would like to bring to the attention of the Office (through the Examiner) that Independent claim 130 is directed to a process for extraction of insulin. The process includes treating expressed insulin present in bound form after the completion of fermentation with water miscible organic solvents selected from the group consisting of ethanol, isopropanol, t-butanol, acetic acid,

dimethylformamide, dimethylsulfoxide, acetonitrile, dioxan, ethylene glycol, and propylene glycol.

Applicant has amended the claim 130 restricting water miscible organic solvents to a group selected from ethanol, isopropanol, acetic acid, dimethylformamide, dimethylsulfoxide, acetonitrile, dioxan, ethylene glycol, and propylene glycol. All of the enlisted solvents are miscible with water.

The selected solvents possess a common property i.e. water miscibility. Therefore, these solvents belong to the same group of water miscible organic solvents, which are polar in nature. (Abstract: Olofsson, L., Pernilla, S., Ian, N. Influence of water miscible organic solvent on α-chymotrypsin in solution and immobilized on Eupergit CM. Biotechnology Letters, Vol. 28, No. 12, June 2006, pp. 929-935; Vollhardt KPC., Schore NE. Organic Chemistry Structure and Functions, 4th Edition, W.H. Freeman and Company, New York 2003; Page No. 228,249-250, 279, 280, 281; Lange, NA. Lange's Handbook of Chemistry. 13th Edition.McGraw-Hill Book Company; 10-103-116; http://virtual.yosemite.cc.ca.us/smurov/orgsoltab.htm; http://organicdivision.org/organic_solvents.html).

The selected solvents though belong to different structural class, but these solvents possess same property of being miscibile in water.

S. No.	Solvent	Formula	Solubility in water (g/100g)	Relative polarity
1.	Ethanol	C_2H_6O	Miscible	0.654
2.	Isopropanol	C_3H_8O	Miscible	0.546
3.	t-butanol	$C_4H_{10}O$	Miscible	0.389
4.	Acetic acid	$C_2H_4O_2$	Miscible	0.648
5.	Dimethylformamide	C_3H_7NO	Miscible	0.404
6.	Dimethylsulfoxide	C_2H_6OS	Miscible	0.444
7.	Acetonitrile	C_2H_3N	Miscible	0.460
8.	Dioxan	$C_4H_8O_2$	Miscible	0.164

9.	Ethylene glycol	$C_2H_6O_2$	Miscible	0.790
10.	Propylene glycol	$C_3H_8O_2$	Miscible	0.716
11.	Water	H_2O	Miscible	1

(Refernce: http://virtual.yosemite.cc.ca.us/smurov/orgsoltab.htm)

The general rule of solubility (Solute-Solvent) or miscibility (solvent-solvent) states "like dissolve like". As the selected solvents are polar in nature and belong to the same group of polar solvent as water, these solvents are miscible with water. Thus, the selected water miscible organic solvents are obvious variants of each other in terms of water miscibility.

A prior art search for polar water miscible organic solvents will include the selected solvents. Further, restricting the claims to isopropanol will unnecessary limit the scope of the patent application as the present application enables the extraction of insulin using all the specified solvents (Examples 1-2).

It is therefore evident from the facts and reasoning provided above that the claims have a single general inventive concept, i.e., the process for recovering insulin from culture medium/broth using water miscible organic solvents. Accordingly, reconsideration and withdrawal of the restriction requirement is respectfully requested.

I-Claim rejection - 35 USC § 102

In the most recent Office action, the Examiner rejected the claims 130, I3I, 135-I37, 141 and I42 under 35 USC § 102(e) as being anticipated by Annibali (USPN 7,091,032).

In view of the present amendment, Applicants respectfully traverse the present rejection and request reconsideration and allowance of the pending claims to the extent that it may be considered that the present rejection is applicable to the amended claims, for at least one of the following reasons. None of these references teach or suggest each and every limitation recited in the pending claims. Applicants have rewritten the claims to define the invention more particularly and distinctly so as to overcome the technical objections and rejections and define the invention patentably over the prior art.

The Examiner contends that Annibali as disclosing a process for the recovery of recombinant insulin including treating a culture medium comprising cells for expressing insulin with a water miscible solvent and isolating the insulin from the mixture (col. 25 ,lines I -50). In support of his argument, the Examiner quotes col. 25, In. 17-26 of Annibali

> "Once the growing phase of the biomass was completed, the cells were kept without feeding for half an hour and the production phase begun. During said phase pH was regulated from 3.5 to 5.5, and 100% methanol was added plus 12 ml/l of trace salts, at a rate of 1.2 ml/l/h. This last phase can be extended for up to 96 hours. Variations may be introduced by selecting adequate times for adding methanol to the culture, changing methanol concentration and using a double feed of glycerol/methanol, for further improving the production process."

Thus, according to the Examiner when the methanol initially hits the culture, expression of insulin in some cells begins. The induction of insulin expression occurs before the entire miscible solvent addition step, which can take place for up to 96 hours, is complete. Accordingly, Annibali teaches a method including the steps of adding methanol to induce expression and adding

methanol to cells already expressing insulin. Further to this, the examiner adds that as the instant claim 130 is written in open form it does not exclude additional unrecited method steps.

Applicants respectfully traverse the Examiner's rejections under 35 USC § 102(e) as being anticipated by Annibali (USPN 7,091,032). To anticipate a claim, the reference must teach each and every element of the claim

According to 2131 of the MPEP, "A claim is anticipated only if each and every element is set forth in the claim is found either expressly or inherently described in a single prior art reference." (Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053, Fed. Cir. 1987).

The presently amended claim 130 is directed to a process for extraction of insulin. The process includes treating the expressed insulin, which is present in bound form after the completion of fermentation in expressing cell, with water miscible organic solvents selected from the group consisting of ethanol, isopropanol, t-butanol, acetic acid, dimethylformamide, dimethylsulfoxide, acetonitrile, dioxan, ethylene glycol, and propylene glycol. The process as claimed in the present invention is performed after the completion of fermentation and before the cell clarification (emphasis added).

Annibali teaches the addition of methanol to induce the expression of insulin in Pichia. Annibali teaches the addition of methanol to fermenation broth culture. It is known in the art that the methylotropic yeast Pichia pastoris will utilize the methanol added to the fermentation broth as a carbon and energy source. It is so well known to those of ordinary skill in the arts that the addition of any alcohol, other than methanol will not induce expression in Pichia as it can only metabolize methanol.

Annibali, however, fails to describe or suggest the use of water miscible organic solvents that include ethanol, isopropanol, t-butanol, acetic acid, dimethylformamide, dimethylsulfoxide, acetonitrile, dioxan, ethylene glycol, and propylene glycol to extract the insulin present in bound form from the cells. Applicant has recognized that insulin present in the bound form in cells can be extracted with water miscible organic solvents such as the ones disclosed in the

present process. Unlike the process of Annibali, the present invention teaches the use of water miscible organic solvents to extract the insulin present in the bound form from the cells.

Annibali also fails to describe or suggest the addition of any water miscible organic solvent to the broth culture after the completion of fermentation and before the isolation of insulin. On the other hand, the present invention teaches the addition of water miscible organic solvents selected from the group consisting of ethanol, isopropanol, t-butanol, acetic acid, dimethylformamide, dimethylsulfoxide, acetonitrile, dioxan, ethylene glycol, and propylene glycol to the broth obtained after completion of fermentation to extract insulin present in bound form from the cells.

In fact, Annibali does not even mention or recognize the presence of bound insulin in the expressing cells. Annibali does not teach or suggest the extraction of this bound insulin present in the expressing cells with water miscible organic solvents. The only two solvents used by Annibali are methanol and glycerol. It is well known to those of ordinary skill in the art that these two solvents are components of the feed or derepression media used to sustain the growth of Pichia and to induce the expression of insulin. It is also known in the art that Pichia can utilize only simple methanol as energy source.

Furthermore, Annibali uses only 1.2 ml/l/h (approximately about 1% v/v) as the amount of methanol added to fermentation broth culture, which is quantitatively very less. One of ordinary skill in the art very well recognizes that this amount is not sufficient for extraction of expressed insulin. The methanol in such a concentration (1.2 ml/l/h) would only be useful for the induction of alcohol oxidase promoter. Even if, presumingly methanol added to the fermenation media will extract the bound insulin, there will be no significant difference in the yield obtained. On the other hand, the amount of water miscible solvent added to the fermentation broth culture in the present invention is quantitatively very high i.e. about 10%v/v to about 40% v/v, which is almost 10-40 times more than the amount of methanol added to culture broth in Annibali. The addition of water miscible organic solvent in a concentration range of about 10%v/v to about 40%

v/v as is used in the present invention results in approximately doubling the yield of the product.

During the process of production of insulin, the expressed insulin is present in two forms in broth culture:

- Soluble form – Insulin in soluble form is secreted in extracellular medium
- Bound form- Insulin remain bound to cellular surfaces or to the debris of expressing cells

The present invention is directed to extract the expressed insulin, which is present in the bound form. In the present process, after the completion of fermentation, the broth obtained from fermentation is treated with water miscible organic solvents selected from the group consisting of ethanol, isopropanol, t-butanol, acetic acid, dimethylformamide, dimethylsulfoxide, acetonitrile, dioxan, ethylene glycol, and propylene glycol. This treatment with water miscible organic solvents results in extraction of bound insulin, which is usually lost during the cell clarification process.

Thus, the present process attempts to simultaneously isolate insulin present in the soluble and bound form by treating the fermentation broth culture obtained after the production phase is over with 10-40% v/v of water miscible organic solvents. The water miscible organic solvent extracts the insulin present in the bound form. Thus, during the isolation not only the insulin present in the soluble form (x quantity) but also the bound insulin (y quantity), which is extracted using water miscible organic solvent gets recovered. This leads to the increase in overall yield (x+y) of the insulin.

Applicants have amended claim 130 to further clarify the subject matter. Presently amended claim 130 is directed to a process of extraction which is performed after the completion of fermentation to extract the insulin present in bound form with the use of water miscible organic solvent. Thus, the present invention only relates to a process of extraction and not to the expression of insulin.

Further, the amended claim 130 includes water miscible solvents selected from the group consisting of ethanol, isopropanol, t-butanol, acetic acid,

dimethylformamide, dimethylsulfoxide, acetonitrile, dioxan, ethylene glycol, and propylene glycol. On the other hand, Annibali teaches addition of methanol to the growing cells mass. Annibali does not teach addition of any other claimed water miscible organic solvent to the growing cell mass. Thus, the present objection of adding methanol to cell culture mass stands moot in light of the amended claim 130.

As stated above, none of these references relied on by the Examiner teach or suggest each and every limitation recited in the pending claims.

A single prior art reference anticipates a patent claim only if it expressly or inherently describes each and every limitation set forth in the patent claim. Trintec Industries, Inc. v. Top-U.S.A. Corp., 295 F. 3d 1292, 63 USPQ2d 1597 (Fed.Cir.2002); See Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2D 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the....claim. Richardson v. Suzuki Motor Co., CO F. 2d 1226, 9 USPQ2d 1913, 1920 (Fed. Cir.1989).

Accordingly, this rejection should be withdrawn.

II. Claim rejections - 35 USC § 103

Rejection based on over US 7,091,032 (Annibali) in view of Willis (Modern Drug Discov., 2001, 4, 43-44)

In the most recent Office action, the Examiner rejected claim 140 under 35 USC § 103(a) as being unpatentable over Annibali (USPN 7,091,032), as applied to claims 130, 131, 135-137, 141 and 142 above, in view of Willis (Modern Drug Discov.,2001, 4, 43-44).

The Examiner contends that Annibali as disclosing a method including the steps of adding methanol to induce expression and adding methanol to cells already expressing insulin. With respect to claim 140, Annibali does not teach the use of expanded bed chromatography. Willis teaches that expanded bed chromatography is a technique that combines the step of sample preparation with the first stage of chromatography, and is advantageous for use in methods for purification of recombinantly expressed proteins in cells. Thus, the invention

as a whole is clearly obvious to one of ordinary skill in the art.

To establish a prima facie case of obviousness, there must be some teaching, suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine references to arrive at claimed invention. (2143 MPEP-Basic Requirements of a Prima Facie Case of Obviousness)

The recent case law establishes that "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (*KSR*, 550 U.S. 82 USPQ2d at 1396).

The presently amended claim 140 discloses the isolation of insulin from the fermentation broth using a cation exchange chromatography in expanded bed mode. Amended claim 140 is dependent on amended claim 130, thus imports all the limitations of amended claim 130.

The presently amended claim 130 is directed to a process for extraction of insulin. The process includes treating expressed insulin, which is present in bound form after the completion of fermentation in expressing cell, with water miscible organic solvents selected from the group consisting of ethanol, isopropanol, t-butanol, acetic acid, dimethylformamide, dimethylsulfoxide, acetonitrile, dioxan, ethylene glycol, and propylene glycol. The extraction of bound insulin using water miscible organic solvents results in overall increase in the yield of insulin.

Annibali teaches addition of very small amount of methanol (about 1%) to fermentation broth culture to induce expression of insulin in Pichia pastoris. The methylotropic yeast Pichia pastoris uses the added methanol as a carbon and energy source (See Col. 5, lines 30-21 of Annibali).

It is well known to those of ordinary skill in the art that the sole purpose of adding methanol to the media containing Pichia pastoris is as a carbon and energy source to sustain the growth of yeast. It is also known in the art that Pichia pastoris cannot metabolize or utilize alcohol other than methanol. It is also known in the art that glycerol is the common component of derepression

solution, which is used to induce the expression of any gene of heterologus protein such as insulin.

Annibali, however, fails to describe or suggest a process for extraction of bound insulin using water miscible organic solvents. Annibali also fails to teach or suggest treating the broth culture obtained after fermentation with water miscible organic solvents. Annibali does not disclose a step of extraction after the production phase (completion of fermentation) and before the isolation of expressed insulin.

Annibali does not teach or suggest the use of water miscible organic solvents to increase the overall yield of insulin. Annibali only teaches the use of methanol and does not teach the use of water miscible organic solvents as disclosed in the present invention.

Moreover, the amount of water miscible solvent used in Annibali (less than 1% v/v) is quantitatively less than the amount of alcohol used in the present invention (10% v/v to 40% v/v). It is known to those of ordinary skill in the art that the amount of methanol used in Annibali during the fermentation is insufficient for the extraction of bound insulin.

Willis is a general disclosure of technology and mechanics involved in expanded bed adsorption chromatography (EBA) and its application. Willis discloses enhanced recovery of recombinant proteins such as monoclonal antibodies when expanded bed chromatography is used.

Willis, however, fails to describe or suggest the use of expanded bed mode chromatography for the isolation of insulin. Further, it does not disclose the extraction of bound insulin by adding one or more water miscible solvents selected from the group consisting of ethanol, isopropanol, t-butanol, acetic acid, dimethylformamide, dimethylsulfoxide, acetonitrile, dioxan, ethylene glycol, and propylene glycol to fermentation broth culture medium after the production phase is over for increasing the recovery of any peptide or protein.

The overall increase in the yield in the present invention is not because of the use of expanded bed chromatography. It is the use of water miscible organic solvents, which amounts to the increase in the overall yield of insulin as a result

of extraction of bound insulin.

Examiner relied on two references Annibali and Willis for supporting the rejection on obviousness. Annibali does not teach a process of extraction of insulin using 10-40% v/v water miscible organic solvents, which is added after the completion of fermentation and before the isolation of the expressed insulin. Willis does not teach the recovery of any polypeptide from the culture medium/broth using water miscible solvents. The combination of Annibali and Willis would have taught one of skill in the art to use methanol in the fermentation media and the isolation of expressed insulin using expanded bed chromatography with the loss of insulin present in the bound form in the cells. Thus, one of skill in the art would not be motivated to combine the Annibali and Willis in the manner purported by the examiner.

"One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." (In Re fine, 837, F. 2d 1071, 1075, 5 USPQ 2d, 1596, 1600, Fed. Cir.1988).

In summary, neither Annibali nor Willis, taken separately or in combination, disclose a process for extraction of insulin, wherein the process includes treating expressed insulin present in bound form after the completion of fermentation with water miscible organic solvents selected from the group consisting of ethanol, isopropanol, t-butanol, acetic acid, dimethylformamide, dimethylsulfoxide, acetonitrile, dioxan, ethylene glycol, and propylene glycol. Accordingly, claim 130 is allowable over Annibali and Willis taken separately or in combination.

Examiner rejected the claims 132 and 133 under 35 USC § 103(a) as being unpatentable over Annibali (USPN 7,091,032), as applied to claims 130, 131, 135-137, 141 and 142 above in further view of Scopes et al. (Protein Purification: principles and Practice, Springer, new York, 1994, pp 157-71) and Gerlough & Bates (J. Pharm. Exp. Therapeutics, 1932, Vol. XLV,

No. 1, pp. 19-51).

Examiner quotes that Annibali does not teach the use of other water miscible organic solvents to purify the recombinant insulin. Gerlough and Bates teach a method of purifying insulin comprising alcohol (more than 60%) precipitation of insulin obtained from minced beef pancreas. Scopes teaches that the method of protein precipitation by water miscible solvents has been used since early days of protein purification. Thus, it would be obvious to a skilled artisan to add a precipitation step as an additional step to the purification protocol taught by Annibali, according to the teachings of Gerlough & Bates and Scopes.

Amended claim 132 and 133 are dependent on amended claim 130. Claim 132 discloses the use of isopropanol as a water miscible organic solvent. Claim 133 discloses that the water miscible organic solvent is used at a concentration range from about 10% (v/v) to about 40% (v/v).

The presently amended claim 130 is directed to a process for extraction of insulin. The process includes treating expressed insulin, which is present in bound form after the completion of fermenation in expressing cell, with water miscible organic solvents selected from the group consisting of ethanol, isopropanol, t-butanol, acetic acid, dimethylformamide, dimethylsulfoxide, acetonitrile, dioxan, ethylene glycol, and propylene glycol.

Annibali teaches the addition of very small amount of methanol (about 1%) to fermentation broth culture to induce expression of insulin in Pichia pastoris. The methylotropic yeast Pichia pastoris uses the added methanol as a carbon and energy source (See Col. 5, lines 30-21 of Annibali).

Annibali fails to describe or suggest a process for extraction of bound insulin using water miscible organic solvents. Annibali does not teach or suggest treating the broth culture obtained after fermentation with water miscible organic solvents. Annibali also does not disclose a step of extraction after the production phase (completion of fermentation) and before the isolation of expressed insulin.

Annibali does not teach or suggest the use of water miscible organic solvents to increase the overall yield of insulin. Annibali only teaches the use of methanol and does not teach the use of water miscible organic solvents as

disclosed in the present invention. Annibali does not teach the use of water miscible organic solvents in a concentration range of 10% v/v to 40% v/v.

Scopes teaches that the method of protein precipitation by the use of water miscible solvents. Gerlough and Bates teach purification by fractional precipitation of insulin with alcohol.

Scopes and Gerlough & Bates do not teach or suggest the use of water miscible organic solvents to extract bound insulin from the cells present in the broth obtained after the completion of fermentation.

Applicant would respectfully like to draw the examiners attention to the fact that the present invention does not relate to a process of purification of insulin by precipitation. The present invention does not involve precipitation of insulin using water miscible organic solvents. The purpose of adding water-soluble organic solvents is to extract the insulin, which is bound to cellular organelle or debris. The addition of water-soluble organic solvent does not result in precipitation of insulin present in the fermentation broth culture. The intent of adding water-soluble organic solvent is not to precipitate the insulin present in the fermentation broth culture.

Further, the amount of water miscible solvent used in the present invention varies from about 10% to about 40%v/v, which is less than the amount of alcohol used for precipitation of insulin (more than 50%).

Annibali teaches the use of methanol as a carbon source to induce the expression in Pichia pastoris. Annibali does not teach the use of water miscible solvents for increasing the extraction of bound insulin. Scopes is a generic disclosure. Gerlough and Bates do not teach a process for enhancing the recovery of insulin by treating the culture medium/broth using water miscible solvent without precipitating the protein. A skilled artisan would not be motivated to combine the aforementioned prior arts in the manner purported by the examiner.

In summary, neither Annibali, Scopes nor Gerlough and Bates, taken separately or in combination, disclose a process for extraction of insulin, wherein the process includes treating expressed insulin present in bound form after the

completion of fermentation with water miscible organic solvents selected from the group consisting of ethanol, isopropanol, t-butanol, acetic acid, dimethylformamide, dimethylsulfoxide, acetonitrile, dioxan, ethylene glycol, and propylene glycol. Accordingly, claim 130 and dependent claims 132 and 133 are allowable over Annibali, Scopes, and Gerlough and Bates taken separately or in combination.

As noted above that the Office Action fails to specifically address even the expressly recited features of the pending independent and dependent claims. Under the Office's policy of compact prosecution, each claim should be reviewed for compliance with every statutory requirement for patentability in the initial review of the application. (MPEP §707.07(g)). Thus, it is submitted that the Office's failure constitutes a failure to expeditiously provide the information necessary to resolve issues related to patentability that prevents the Applicant from, for example, presenting appropriate patentability arguments and/or rebuttal evidence. (See The Official Gazette Notice of November 7, 2003). Additionally, it is submitted that the Office's failure needlessly encourages piecemeal prosecution, which is to be avoided as much as possible. (MPEP §707.07(g)). Accordingly, in the event that the Examiner maintains the rejection of any of the independent and/or dependent claims, Applicant respectfully requests, in the interests of compact prosecution, that the Examiner apply art against each feature of each rejected independent and dependent claims, on the record, and with specificity sufficient to support a prima facie case of obviousness.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

It is well known that in order for any prior-art references themselves to be validly combined for use in a prior-art § 103 rejection, *the references themselves* (or some otherprior art) must suggest that they be combined. E.g., as was stated in In re Sernaker, 217 U.S.P.Q. 1, 6 (C.A.F.C. 1983):

"[P]rior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantages to be derived from combining their teachings." That the suggestion to combine the references should not come from applicant was forcefully stated in Orthopedic Equipment Co. v. United States , 217 U.S.P.Q. 193, 199 (C.A.F.C. 1983):

"It is wrong to use the patent in suit [here the patent application] as a guide through the maze of prior art references, combining the right references in the right way to achieve the result of the claims in suit [here the claims pending]. Monday morning quarterbacking is quite improper when resolving the question of nonobviousness in a court of law [here

the PTO]." As was further stated in Uniroyal, Inc. v. Rudkin-Wiley Corp., 5 U.S.P.Q.2d 1434 (C.A.F.C. 1988), "[w]here prior-art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself

... *Something in the prior art must suggest the desirability and thus the obviousness of making the combination.*" [Emphasis supplied.]

In line with these decisions, the Board stated in Ex parte Levengood, 28 U.S.P.Q.2d 1300 (P.T.O.B.A.&I. 1993):

"In order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, or in the form of generally available knowledge, that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the, applied references in the proposed manner to arrive at the claimed invention. ...

That which is within the capabilities of one skilled in the art is not synonymous with obviousness. ... That one can *reconstruct* and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion unless that logic and reasoning also supplies sufficient impetus to have led one of the ordinary skill in the art to combine the teachings of the references to make the

claimed invention.... Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that 'would lead' that individual 'to combine the relevant teachings of the references.' ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done."

In the present case, there is no reason given in the last Office action to support the proposed combination. However the fact that references teach one or more limitations is not sufficient to gratuitously and selectively suggest that the one would be led to substitute parts of one reference for a part of another reference in order to meet applicants' novel claimed combination.

The references relied upon fail to provide an adequate basis in evidence to support the Examiner's initial conclusion of obviousness. In short there must be more than merely establishing that the individual components exist in the prior art. There must be something , found in the prior art which would have suggested , led or motivated one skilled in this art to bring those individual components together in the manner presently claimed. The present rejection lacks this aspect.

It is respectfully requested that these rejection be reconsider and withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance and notification to that effect is earnestly requested. If desired, the examiner is invited to conduct a telephone conference to expedite the prosecution of the subject application. In such a case, the examiner is invited to call the undersigned attorney.

Should any official at the United States Patent and Trademark Office

deem that any further action by the Applicants or Applicants' undersigned representative is desirable and/or necessary, the official is invited to telephone the undersigned at the number set forth below.

The Commissioner is herby authorized to charge any fees which may be required regarding this application under 37 CFR §§ 1.16-1.17 or credit any overpayment, to deposit account No. 503321. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, or otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 503321.

Respectfully submitted,

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